Remarks/Arguments

Claims 1, 2, 4-8, 10-16 and 18-28 are pending in the application. Reconsideration is respectfully requested.

Priority

Applicants have amended the specification to recite that the present application is a national stage application of International Application No. PCT/ US2003/27618, which designated the United States and was filed on September 4, 2003, which is a continuation-in-part of United States Patent Application Serial Number 10/392,333, filed March 19, 2003. The provisional applications are retained in the paragraph to ensure that the incorporation by reference is maintained. The Examiner states that the presently claimed application is not entitled to the priority of the 5 provisionals referenced therein. Applicants agree and respectfully submit that priority has not been claimed to the provisional applications.

Claim Rejections-35 U.S.C. §112

The Examiner has rejected claims 8, 10-16 and 18-21 under 25 U.S.C. §112, second paragraph as being indefinite. The Examiner states that the term "fine particle fraction" as used in claim 8 fails to disclose the aerodynamic diameter of the particles and therefore any particle size will satisfy the limitation of this claim. The Examiner states that Applicant's previous arguments that the term "fine particle fraction" are clearly defined on page 4, line of the specification still does not define invention of the claim properly. The Examiner, citing *In re Van Geuns* states that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. Applicants maintain that no additional limitations are required to be read into the specification. The term "fine particle fraction" is a term of art and is *equivalent* to a recitation of the aerodynamic diameter of a particular mass of particles comprising that aerodynamic diameter. The present application defined that the aerodynamic diameter

associated with the term "fine particle fraction" as used in the present specification and claims is 3.4 microns. As stated in MPEP §2173.05:

> The meaning of every term used in a claim should be apparent from the prior art or from the specification and drawings at the time the application is filed. Applicants need not confine themselves to the terminology used in the prior art, but are required to make clear and precise the terms that are used to define the invention whereby the metes and bounds of the claimed invention can be ascertained. During patent examination, the pending claims must be given the broadest reasonable interpretation consistent with the specification. *In re Morris*, 127 F.3d 1048, 1054, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997); *In re Prater*, 415 F.2d 1393, 162 USPQ 541 (CCPA 1969). See also **MPEP § 2111 - § 2111.01**. When the specification states the meaning that a term in the claim is intended to have, the claim is examined using that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art. *In re Zletz*, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989).

In the present case, the specification clearly states the meaning of the term "fine particle fraction" as is used in claim 8. It is not necessary to "read in" the aerodynamic diameter and in fact, to include the aerodynamic diameter in claim 8 in addition to the term "fine particle fraction" would be redundant.

The Examiner also rejects claim 15 stating that the term "at least about" is indefinite as it is unclear as to what range is covered by the term "about". The Examiner asserts that the claim lacks clarity as to whether "at least" (minimum) or "about" (broadening limitation, both higher and lower) controls the metes and bounds of the phrase "at least about". First it is noted that claim 15 does not include the phrase "at least about", claim 14 includes this phrase in reference to the percentage by weight of leucine contained in the formulation. Claim 15 includes the phrase "less than about" with reference to the percent by weight of trospium included in the formulation.

The skilled practitioner would clearly understand the metes and bounds of the phrase "at least about" in the context of claims 14 and 15. The fact that the term "about" is inserted before the percent by weight of trospium or leucine merely indicates to the skilled practitioner that the precise percentage can not be articulated given for example, that a measurement of percent by weight is not always a whole number.

According to MPEP §2173.05(b)(A), the term "at least about" in a claim was determined to be indefinite when there was close prior art and there was nothing in the specification, prosecution history or the prior art to provide any indication as to what range of specific activity is covered by the term "about". However the facts in the present application are very different. There is no close prior art that discloses a trospium formulation comprising leucine in any percent by weight range. In addition, the specification itself discloses on page 4, lines 26-32 that preferred formulations contain about 5% trospium and between about 85-90% by weight of leucine. The specification also discloses on pages 10-12 formulations comprising 5% by weight of trospium and 85-90% by weight of leucine had the desired FPF of less than 3.4 (Table 4 page 12) and achieved effective therapy for at least 10 hours (Figure 3). Thus the specification provides the skilled practitioner with more than enough information to readily understand what specific activity is included in the term "at least about" as it is used in the claims. Indeed, at least 71,000 US patents have been granted to date with this term. There is no reason to set forth on this record that such language should not be permitted here. The scope of the claims is clear, and the rejection is improper. Withdrawal of the rejection is respectfully requested.

Claim Rejections 35 U.S.C. §102

Claims 1, 4, 5 and 22-26 are rejected under 35 U.S.C. §102(b) as being anticipated by Freund et al. (U.S. Pat. App. Pub. No. 2001/0008632). The Examiner states that Freund teaches aqueous aerosols of anticholinergic agents including trospium chloride, ipratropium bromide, formoterol and fenoterol for inhalation in the treatment of respiratory passage diseases. The Examiner also states that Freund also teach an active agent concentration range of 10 mg/100ml to 2000 mg/100 ml and a nebulizer delivering 12 ml of concentrate per operation which the Examiner has calculated to be between 1.2 mcg and 2400 mcg per operation. The Examiner further notes that claim 1 of the instant application recites a functional limitation of "effective therapy of at least 10 hours" and that the instant specification appears to demonstrate that both aqueous and dry powder formulations of trospium are therapeutically effective for at least 10 hours. The Examiner concludes that it appears that the 10 hour effective duration of action of

trospium is independent of its formulation and one would anticipate that the aqueous trospium formula taught by Freund would have a similar therapeutically effective duration of action, absent evidence to the contrary. Applicants respectfully disagree.

While Applicants have shown that the 10 hour duration of therapeutic effectiveness can be achieved with both an aqueous formulation and a dry powder formulation, this is not tantamount to a showing that all aqueous or dry powder formulations comprising trospium achieve this same effect. As shown in Figure 1b, there is a dose response associated with trospium formulations of various doses. As shown in Figure 1b, trospium dosages as low as 1 and 2 mcg when administered according to the methods described in the specification begin to lose their broncoprotection at 5 hours and the 1 mcg dose is almost back at the pre-TrCl treatment baseline by 15 hours. In relying on the theory of inherency, the Examiner must provide a factual basis to reasonably support that the allegedly inherent characteristic necessarily flows from the teachings of the cited reference each and every time; the mere fact that a certain thing may result from a given set of circumstances is simply not sufficient (MPEP §2112; *Ex parte Levy*, 17 USPQ2d 1461 (Bd. Pat. App. & Inter. 1990); *In re Robertson*, 169 F.3d. 743, 745 (Fed Cir. 1999). The skilled person would not necessarily choose trospium from amongst the list of over 100 drugs named in Freund on the one hand and would also not necessarily choose the dosage ranges which would provide the claimed 10 hour therapeutic benefit on the other hand. Therefore, the Examiner has failed to establish that Freund inherently anticipates the presently claimed invention. Withdrawal of the rejection under this section in view of Freund is respectfully requested.

The Examiner rejects claims 1, 2 and 4-7 under 35 U.S.C. §102(e) as being anticipated by Richards (U.S. Patent Application Pub. No. 2003/0158176). The Examiner states that Richards teaches anticholinergic agents including the compound trospium are useful for the treatment of acetylcholine-mediated disorders including the treatment of chronic obstructive pulmonary disease (COPD) and asthma. The Examiner states that Richards teaches the administration of these agents by inhalation in the form of an aerosol or dry powder at dosage ranges between 10 μg to 1000 μg which encompasses the instantly claimed dose range of 200 μg to 800 μg. Applicants respectfully disagree.

Richards does not disclose or suggest the use of any dosage or formulation *of trospium* for treating a disease characterized by a constrictive airway via inhalation. None of the compounds disclosed and tested by Richards is trospium. Trospium is referenced by Richards as an example of a *known* antimuscarinic agent in paragraphs 0091 and 0092. No other information is provided by Richards with regard to trospium. Richards asserts that the anti-muscarinic compound genus and species disclosed and tested in Richards are novel and thus do not include trospium. A comparison of the chemical structure of trospium (Exhibit A; structure of trospium from Wikipedia) with the structure of anti-muscarinic compounds disclosed and tested in Richards establishes this fact. Therefore, Richards does not anticipate the presently claimed invention. Withdrawal of the rejection under this section in view of Richards is respectfully requested.

Claim Rejections-35 U.S.C. §103

The Examiner has rejected claims 1, 2, 4, 5, 22-26 and 28 are rejected under 35 U.S.C. §103(a) as being unpatentable over Freund (U.S. Pat. App. Pub. No. 2001/0008632) in view of Richards (U.S. Patent Application Pub. No. 2003/0158176). The Examiner states that Freund does not teach specific respiratory passage disease. The Examiner states that Richards teaches that the dose depends on many factors including potency of the compound, the age and weight of the patient and the severity of the disease. The Examiner asserts that one of ordinary skill would have optimized the dose taught by Freund to maximize the therapeutic effects and minimize the deleterious effects of the active agent. The Examiner then states that the skilled person would have found it obvious to combine these two teachings to treat diseases such as COPD by inhalation of trospium because Freund teaches the usefulness of trospium and formoterol for treating respiratory passage disease and Richards teaches COPD and asthma as two respiratory diseases effectively treated by trospium. The Examiner concludes that one would have been motivated to administer the active agents via inhalation to treat the respiratory system to minimize the amount agent administered systemically thereby avoiding undesirable effects and to improve upon the known methods of treatment for COPD and asthma.

The Examiner disagrees with Applicants' arguments in their response dated January 10, 2008, with regard to the combination of Freund and Richards. In that response, Applicants argued that the Examiner has not provided motivation as to why one would pick trospium from a list of over 100 active ingredients disclosed in paragraphs 0015-0045 of Freund in order to prepare an optimized formulation having sustained effective therapy for at least 10 hours. The Examiner asserts in response that Richards teaches trospium to be an anticholinergic agent and provides ample motivation to select trospium as one of 4 anticholinergic agents disclosed by Freund as an active agent in the Freund reference.

However, the Examiner has still not accounted for the fact that Richards simply teaches nothing about dosage or formulation or hours of therapeutic effectiveness of *trospium*. Trospium is not the compound formulated or tested in Richards. Trospium is an anti-muscarinic and Richards discloses the synthesis and testing of novel anti-muscarinics. However, the class of anti-muscarinics is a functional class definition and not a structural class definition. Compounds that behave as anti-muscarinics may be very diverse structurally and functionally even with regard to their anti-muscarinic activity and potency. Exhibit A clearly shows that the structure of trospium is different from the genus and species disclosed in Richards. Thus the broncodilatory effects of various dosages and formulations of trospium are not disclosed in Richards. Given the compounds in Richards are structurally and likely functionally different from trospium there is no basis for the Examiner's assumption that Richards provides any information with regard to the optimization of dosages and formulations of *trospium* which achieve effective therapy for at least 10 hours, alone or in combination with Freund.

Furthermore, Freund does not teach or disclose the therapeutic effectiveness or hours of therapeutic effectiveness of any of the active ingredients listed therein. Freund's alleged discovery is that the spraying anomalies of aqueous pharmaceutical solutions for inhalation using a nebulizer can be reduced or minimized by the use of a complexing agent in the aqueous preparation. The therapeutic effectiveness of the solutions prepared by Freund is never tested. Only the ability of EDTA to minimize nebulizer anomalies is tested.

In view of the above discussion, the Examiner has failed to establish that the presently claimed invention is *prima facie* obvious in view of the cited combination of references. Withdrawal of the rejection under this section is respectfully requested.

The Examiner has rejected claims 1, 2, 4-8, 10-13, 15, 18-28 under 35 U.S.C. §103(a) as unpatentable over Freund (U.S. Pat. App. Pub. No. 2001/0008632) in view of Richards (U.S. Patent Application Pub. No. 2003/0158176) as applied to claims 1, 2, 4, 5, 22-26 and 28 above, and further in view of Bernstein (U.S. Patent Application Pub. No. 2004/0105821). The Examiner states that Bernstein teaches particulate sustained release pharmaceutical formulations for inhalation useful in treating asthma and COPD among others. The Examiner states that the sustained release formulation provides local or plasma concentrations at nearly constant values over a period of release allowing patients to take the treatments one or twice daily. The Examiner notes that although Bernstein does not teach trospium *per se*, they do teach anticholinergic agents in general and that Freund discloses trospium and ipratropium. The Examiner asserts that one of ordinary skill in the art would have understood (especially in light of the teaching of Freund) that one known anticholinergic agent (i.e. trospium) could be substituted for another (i.e. ipratropium) with reasonable expectation of success. Applicants disagree.

Freund does not teach or disclose the therapeutic effectiveness or hours of therapeutic effectiveness of the active ingredients listed therein. Freund's alleged discovery is that the spraying anomalies of aqueous pharmaceutical solutions for inhalation using a nebulizer can be reduced or minimized by the use of a complexing agent in the aqueous preparation. The therapeutic effectiveness of any of the solutions prepared by Freund is never tested. Only the ability of the complexing agent to minimize nebulizers with spray anomalies is tested with a formulation of ipratropium bromide and EDTA. Note that the other solutions of active ingredients listed in the table in paragraph 0051 are not even tested for nebulizer anomalies. Clearly one skilled in the art would not have "understood" that one anticholinergic agent such as trospium could be substituted with another such as ipratropium with any reasonable expectation of therapeutic effectiveness for any time frame based on Freund.

Likewise, Bernstein is directed to particle formulation and does not provide any evidence of the therapeutic effectiveness of any the hundreds of therapeutic agents listed therein. Only the physical characteristics of the particles prepared therein are tested in the Examples disclosed and the only the regional distribution of particles containing budesonide in the human lung is tested in Example 4. Bernstein provides no information or evidence with regard to the therapeutic effectiveness or hours of therapeutic effectiveness of the formulations or whether such formulations actually provide the extended release properties asserted in Bernstein.

Furthermore, Richards never tests trospium for therapeutic effectiveness over any period of time. As discussed above, Richards tests compounds having chemical structures that are different from trospium. Therefore, the skilled person has no basis to conclude that an inhalable trospium formulation is capable of delivering 10 hours of effective therapy based on the cited combination of references. The Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, withdrawal of the rejection under this section in view of the cited references is respectfully requested.

Information Disclosure Statement

An Information Disclosure Statement is being filed concurrently herewith.

Conclusion

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 251-3509.

Respectfully submitted,

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